REMARKS

Claims 1, 2, 12, 23, 26, 38, and 47-56 are pending. Claims 3-11, 13-22, 24-25, 27-37, and 39-46 are canceled.

1. Applicants appreciate Examiner Prebilic's courtesies extended during a telephonic interview of March 11, 2008, and appreciate Examiner Prebilic's consideration of and comments on Applicant's positions. The discussion of the Ruys reference in relation to the present claims reflects the expressed positions and comments.

2. Claims 1, 2, 12, 23, 26, 38, and 47-56 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The originally filed application indeed disclosed the compositional range of 50:50 to 80:20 stabilized tricalcium phosphate to hydroxyapatite in connection with stabilized tricalcium phosphate. See the original claims 11 and 21. Applicants have amended the specification to reflect the subject matter of the originally submitted claims.

Applicants also point out that while the specification discloses ratios with respect to thin film sintered tricalcium phosphate, these ratios are clearly tracked to embodiments of the claimed invention. Page 13, lines 3-10 of the present specification teaches desired and preferred ranges of compositions, and discloses the influence of temperature on such desired and preferred ranges of composition. The specification then discloses methods for forming bulk powder and granule formulations having a stabilized composition in the "desired" ranges. In particular, Applicants disclose in Procedures 4, 5, and 6 methods of forming powdered and bulk ceramic materials containing stabilizing entities, which are sintered in accordance with Procedure 7. Procedure 7 teaches sintering at particular temperature to achieve the "desired ratios" of alpha tricalcium phosphate and hydroxyapatite selected from the same temperatures disclosed in relation to thin films. As such, one of ordinary skill in the bone replacement ceramic arts would have clearly and unequivocally understood that the Applicants were in possession of the claimed invention at the time the present application was filed, by virtue of clear reference to desired ratios achieved through process conditions as described.

For at least the foregoing reasons, Applicants respectfully submit that the subject matter of the claims is describe in such a way as to convey to one skilled in the bone replacement ceramic arts that the inventors, at the time the application was filed, had possession of the claimed invention. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, first paragraph, rejection.

3. Claims 1, 2, 12, 23, 26, 38, 47, 48 and 50-56 were rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the PTO appears to object to the terms "at least 50:50" and "at least 666:333." Applicants respectfully traverse this rejection.

The terms cited above include ratios as the numerical portion of an inequality statement. Applicants respectfully submit that the ratios are an expression of a rational number and thus, provide clear meaning in the context of the terms objected to by the PTO.

A rational number is a number that can be expressed as a ratio or quotient of two non-serial integers. (See, for example, NumberNut.com glossary, attached). A ratio is a comparison of two numbers or two like quantities by division. As examples of ratios, NumberNut.com offers the ratios: two to three, 2/3, 2 to 3, and 2:3. Accordingly, any rational number can be expressed as a decimal such as 2.0, as a fraction (e.g., 666/333), or as a ratio in colon format (e.g., 666:333). Clearly, one can express an inequality in decimal form (e.g., at least 2.0) and one can express an inequality in terms of a fraction (e.g., at least 666/333). Further, one can express an inequality with equal clarity using a ratio in colon format (e.g., at least 666:333).

For at least the foregoing reasons, Applicants respectfully submit that the phrases "at least 50:50" and "at least 666:333" stabilized tricalcium phosphate to hydroxyapatite are clear and particularly point out and distinctly claim the subject matter which Applicants regard as the invention. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, second paragraph, rejection.

4. Claims 1, 2, 12, 23, 26, 38, and 47 were rejected under 35 U.S.C. 102(b) as being anticipated by Ruys (article entitled "Silicon-doped hydroxyapatite") or, in the alternative under 35 U.S.C. 103(a) as obvious over Ruys alone, and claims 48 to 56 were rejected under 35 U.S.C. 103(a) as being upatentable over Ruys alone. Applicants respectfully traverse these rejections.

Present claim 1 is directed to a bioactive artificial sintered composition for supporting bone selectivity. The composition consists essentially of stabilized tricalcium phosphate and hydroxyapatite at a ratio of at least 50:50 tricalcium phosphate: hydroxyapatite. The stabilized tricalcium phosphate is stabilized with a stabilizing entity selected from the group consisting of silicon entities, aluminum entities, barium entities, titanium entities, germanium entities, chromium entities, vanadium entities, niobium entities, boron entities, and mixtures thereof. The composition is bioactive to support osteoblast bone growth and to support extracellular resorption of the composition by osteoclasts.

Present claim 50 is directed to a bone replacement composition comprising tricalcium phosphate and hydroxyapatite in a ratio of at least 666:333 tricalcium phosphate to hydroxyapatite. The tricalcium phosphate is stabilized with a stabilizing entity selected from the group consisting of silicon entities, aluminum entities, barium entities, titanium entities, germanium entities, chromium entities, vanadium entities, niobium entities, boron entities, and mixtures thereof.

Present claim 55 is directed to a bioactive artificial sintered composition for supporting bone cell activity. The composition includes a stabilized tricalcium phosphate and hydroxyapatite in a ratio of at least 666:333 tricalcium phosphate to hydroxyapatite. The stabilized tricalcium phosphate is stabilized with a stabilizing entity selected from a group consisting of silicon, aluminum, barium, titanium, germanium, chromium, vanadium, niobium, boron and mixtures thereof. The composition is insoluble in physiological fluids of pH 6.4 to 7.3. The composition is bioactive to support osteoblast bone growth and to support extracellular resorption of the composition by osteoclasts.

Turning to the reference, Ruys presented work to determine the feasibility of chemically doping hydroxyapatite with silicon. At all silicon levels hydroxyapatite (HAp) formed and, at high silicon levels, α-tricalcium phosphate (α-TCP) and Si-P-O glass formed. (Ruys, Abstract).

In particular, "both α- and β-TCP were formed, although β-TCP was favoured at low silicon levels and α-TCP was favoured at high silicon levels. Further, at higher silicon concentrations, a broad X-ray diffraction peak with a *d* spacing of 0.16-0.26 nm formed. Since both silicon and phosphorous are oxide glass formers, this peak is a result of the presence of a Si-P-O glass. For progressively higher silicon levels, the glass became the dominant phase. At very high dopant levels, approximate area ratios of the main diffraction peaks of HAp and TCP suggested that the TCP content was slightly greater than the HAp content." (Ruys, page 77, paragraph 3). As such, Ruys discloses that at high silicon levels the TCP content was slightly greater than hydroxyapatite content, but the Si-P-O glass phase was the dominant phase.

High levels of Si-P-O glass and in particular, high levels of silicon outside of the crystal matrix of the calcium phosphate species hinder the bioactivity of the material. As described in the Declaration by Dr. Smith dated November 2, 2007, high levels of silicon produce a material that limits initial cell attachment to the surface. In addition, a cited impartial third party reference clearly states that high levels of silicon inhibit osteoclast activity. (See Best et al. pg. 986). Thus, high levels of silicon, which, as taught by Ruys, leads to the formation of Si-P-O glass as a dominant phase, materially affects the bioactivity of the material in that it inhibits osteoclast activity.

With regard to claim 1, Applicants have used the transitional phrase "consisting essentially of," which limits the scope of a claim to the specific materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention. Clearly, the compositions disclosed by Ruys have a predominant phase of Si-P-O glass for any embodiment having notable α-TCP content, materially affecting the basic and novel characteristics of the claimed invention, namely bioactivity, including osteoclast activity. The PTO is directed to MPEP 2111.03, which is instructive on issues relating to interpretation of "consisting essentially of" language. That section makes clear that Applicants have the burden to establish the identity of basic and novel characteristics; otherwise "consisting essentially of" shall be construed by the PTO to be "comprising." However, Applicants have met this burden by (i) actually *claiming* one of the basic and novel characteristics (i.e., the composition is bioactive), and (ii) providing impartial third party evidence that high silicon content, which Ruys states leads to a predominant glass phase, hinders bioactivity (i.e., see Best et al., pg. 986). Interestingly, the MPEP chose to

cite *In re Janakirama-Rao* (137 USPQ 893, 895-96 (CCPA 1963)) involving facts similar to those at hand, in which excessive silicon content was precluded by consisting essentially of language, based on evidence of deleterious affects of silicone content greater than 0.5 wt%.

The Ruys material does not *consist essentially of* a bioactive, high TCP content material since the high TCP-content materials of Ruys contain notable Si-P-O glass, significantly compromising the bioactivity of the material in terms of osteoclast activity. In this regard and as noted in the Declaration by Dr. Smith dated November 2, 2007, Applicants have found that external Si-containing phases, such as Si-P-O glass, in amounts greater than 20 wt% compromise bioactivity as claimed, that is, "to support osteoblastic bone growth and to support extracellular resorption of said composition by osteoclasts."

In contrast to Ruys, Applicants have discovered a method for producing bone replacement compositions predominantly formed of stabilized calcium phosphate phases without the formation of a significant amount of silicon compounds outside of the calcium phosphate matrices. As noted in the Declaration, the method is significantly different from the method disclosed in Ruys, and the material produced by such a method is different from the material disclosed by Ruys. In particular, the compositions produced by the methods discovered by Applicants are predominantly calcium phosphate compositions and have less than 5 wt% of phases including silicon compounds other than silicon stabilized calcium phosphate compositions, such as less than about 3 wt% silicon compound phases. As further explained in the Declaration, the absence of a significant amount of silicon compositions other than the silicon stabilized calcium phosphate compounds in the presence of stabilized α-TCP permits bioactivity and, in particular, permits balanced osteoblast and osteoclast activity as claimed.

Accordingly, based on the transitional phrase "consisting essentially of," claim 1 clearly precludes the presence of Si-P-O glass in amounts over 20 wt%, and certainly as a "predominant phase" as taught by Ruys. As such, Ruys fails to anticipate claim 1 and claim 1 is not obvious over Ruys because the high TCP content materials of Ruys include Si-P-O glass as a predominant phase.

With respect to claims 2 and 12, Applicants have presented evidence above and in previous responses that Ruys fails to inherently disclose the claimed features.

Turning to independent claims 50 and 55, both claims recite a composition comprising tricalcium phosphate and hydroxyapatite in a ratio of at least 666:333 tricalcium phosphate to hydroxyapatite. Ruys is clearly limited to, at best, TCP content "slightly greater" than the HAp content. A ratio of 666:333 is clearly greater than any ratio fairly derived from the teachings of Ruys.

With respect to Ruys, the PTO asserts that since low dopant levels are only preferred and the concept of high dopant levels is also disclosed, it would have been obvious to make higher dopant materials that would fall within the claimed range. However, Ruys teaches consistently throughout the reference against the formation of materials with high TCP content. For example, on page 71, Ruys states that particular mole ratios should be used "in order to avoid formation of biodegradable TCP (emphasis added)." On page 74 in the last paragraph, Ruys teaches use of stir/boil methods "in order to eliminate TCP from the calcined product (emphasis added)." Further, Ruys teaches on page 77, second paragraph that "TCP is an undesirable phase ... (emphasis added)."

Clearly, Ruys teaches away from the formation of materials that include TCP. As such, one skilled in the bone replacement arts would have been deterred from forming compositions having at least 666:333 stabilized tricalcium phosphate to hydroxyapatite and thus, would not have been motivated to form such a composition.

For at least the foregoing reasons, claims 1-2, 12, 23, 38, and 47-56 are not anticipated by and are patentable over Ruys. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(b) rejection of claims 1-2, 12, 23, and 38.

6. Applicants would like to further clarify the Declaration provided by Dr. Smith. As mentioned during the telephonic interview, Applicants attempted to reproduce the data provided by Ruys by following the experimental procedure outlined by Ruys. Despite a faithful attempt to follow the method steps outlined in Ruys, Applicants were unable to synthesize the hydroxyapatite sample Ruys purportedly formed through the method on page 74. Specifically, Applicants were unable to produce hydroxyapatite material free of tricalcium phosphate phases using the method disclosed by Ruys. Since this material was a starting material used in forming the rest of the materials of Ruys, the inability to produce such a material would lead to errors if

the remaining steps were performed. As such, steps or parameters key to the formation of the samples of Ruys may not have been disclosed in the reference, meaning Ruys is not enabled.

Because Applicants were unable to reproduce the materials of Ruys through the methods disclosed by Ruys, Dr. Smith outlined differences between the methods of the present application and that of Ruys. Such differences may explain why Ruys did not produce the claimed materials and thus, provide evidence as to why the claimed materials are not inherently disclosed by Ruys. Further, Dr. Smith provided impartial third party references in support of the position that the material of Ruys is not bioactive as defined in the present specification and claims.

7. As requested by the PTO, Applicants have disclosed to the PTO the existence of copending Patent Application No. 11/738,052 in an Information Disclosure Statement filed November 2, 2007. In addition, Applicants requested reissue of US 6,323,146 on January 30, 2008, which issued from a continuation-in-part application claiming priority to the present application.

Applicant(s) respectfully submit that the present application is now in condition for allowance. Accordingly, the Examiner is requested to issue a Notice of Allowance for all pending claims.

Should the Examiner deem that any further action by the Applicants would be desirable for placing this application in even better condition for issue, the Examiner is requested to telephone Applicants' undersigned representative at the number listed below.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-3797.

Respectfully submitted,

3.18.08
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characterised using scanning electron microscopy, surface area analysis, porosimetry, density measurement, image analysis, X-ray diffraction, X-ray fluorescence and FT-infrared spectroscopy.

Dense, sintered discs were tested using *in-vitro* cell culture with human osteoblasts and osteoclasts. Investigations have been performed to assess osteoblast proliferation and differentiation: to observe osteoclast formation and activity and, in addition, an evaluation of solution mediated effects on osteoblasts and osteoclasts was made. Assays of lactate dehydrogenase (Vialight, Cambrex, UK) and nucleic acids (CyQuant, Invitrogen, UK) have been performed to determine cell number. Alamar Blue (Serotec, UK) reduction was measured to determine cell growth and alkaline phosphatase activity was assessed in osteoblasts using the substrate 6,8-Difluoro-4-methylumbelliferyl phosphate. Osteoclast number was determined by counting multinucleate cells with an actin ring that had previously been shown to stain for tartrate-resistant acid phosphatase (TRAP) and vitronectin receptor whilst resorption area was determined using scanning electron microscopy.

An in-vivo investigation was also performed using defects c. 1 cm^3 in the femoral condyles of sheep. The defects were filled with granules 1-2 mm in diameter comprising either porous HA and Si-HA (Apapore and Actifuse, supplied by ApaTech), 1-2 mm in diameter or dense granules silicon with a wider range of silison substitutions. The animals were given 3 separate fluorochrome injections to assess the mineral apposition rate and specimens were harvested at 6 weeks. The explanted samples were analysed using microtomography to give quantitative information on bone apposition and bone ingrowth. These data were superimposed on sections stained using toluidine blue and the results were compared.

Results and Discussion

The sintered HA and Si-HA materials were confirmed to be phase pure with the expected levels of silicate substitution. There was optimum cell adhesion on 0.8wt% SiHA (Figure 1). It has been hypothesised that the release of soluble silicon from silicon substituted hydroxyapatite into the extracellular fluid surrounding the cells, either by dissolution or by resorption, is responsible for its stimulatory effect on bone formation either by acting directly on osteoblasts or following osteoclast activation and apatite surface resorption.

We have shown positive effects of silicon (30 microM) on osteoblasts however not on osteoclast formation which was inhibited at high concentrations (500 microM). It has also been hypothesised that osteoclast generation and the production of a resorbed surface influence the subsequent behaviour of osteoblasts and we have provided evidence for this in-vitro.

Data from the in-vivo study obtained from the toluidine blue –stained histological sections showed that that the presence of Si in the HA structure enhanced bone apposition. Sections were also stained for TRAP and the total area of resorbing cells was defined. The data obtained indicated the action of osteoclast cells in advance of osteoblastic activity to lay down new bone. This result is highly significant, since it suggests that our evaluation of the osteogenic nature of materials in-vitro might best be performed on surfaces preconditioned by osteoclasts.